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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING METFORMIN AND N-'2-HYDROXY-3-(1-PIPERIDINYL)-PROPOXY! PYRIDINE-1-OXIDE-3-CARBOXIMIDOYL CHLORIDE

(57) Abstract: The invention relates to orally applicable pharmaceutical composition for the treatment of diabetes mellitus and its complications comprising as active principle a combination of metformin (N,N-dimethylimido-dicarbonimidic diamide) or an acid addition salt thereof and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or an acid addition salt of the racemic or the optically active form thereof. The invention also relates to method of treatment of diabetes mellitus as well as a method of treatment of diabetic neuropathy.

PHARMACEUTICAL COMPOSITION COMPRISING METFORMIN AND N-'2-HYDROXY-3-(1-PIPERIDINYL)-PROPOXY! PYRIDINE-1-OXIDE-3-CARBOXIMIDOYL CHLORIDE

Technical field

The invention relates to pharmaceutical compositions containing a combination of metformin and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride as active agent. The composition of the invention can be used in the therapy of the diabetes mellitus, especially in the therapy of type II (non-insulin dependent, NIDDM) diabetes mellitus and its complications, especially in the therapy of diabetic neuropathy.

Background art

Metformin i.e. 1,1-dimethyl-biguanidin (N,N-dimethylimido-dicarbonimidic diamide) is long since known and widely used biguanidin type antihyperglycemic agent. Unlike other antihyperglycemic agents it does not influence the insulin secretion, however, increases the insulin sensitivity of the tissues, inhibits the hepatic glucose production and reduces the glucose absorption. Metformin is used alone or in combination with other antihyperglycemic agents.

Pharmaceutical compositions containing metformin alone are known from WO 97/02843, a combination of metformin and glibenclamide, a sulfonylurea type antihyperglycemic agent is known from WO 97/17975 and WO 00/03742, combinations of metformin and thiazolidine-dione derivatives are known from WO 98/57634.

The sulfonylurea derivatives stimulate the insulin secretion and thus complete the effect of metformin, the thiazolidine-dione derivatives which are insulin sensitizers strengthen the effect of metformin.

Metformin and nateglinide, a phenylalanine derivative /N-{[trans-4-(1-methylethyl)-cyclohexyl]-carbonyl}-D-phenylalanine) are applied simultaneously in order to hinder the postprandial increase of blood glucose level by nateglinide and thereby reduce the mealtime glucose excursion (Diabetes Care Vol. 23, No 3, March 2000 and Diabetes Care Vol. 23, No 11, November 2000).

The particular effects of active agents are enhanced in the compositions of combined active agents mentioned above, but the said compositions are insufficient to reduce the blood glucose level at a substantial extent, which results in need of regular administration of insulin after a period of transition as the illness progresses. An other disadvantage of combined compositions containing metformin and a sulfonylurea type active agent is that they are not safe as to the exclusion of occurence of hypoglycemia.

Pharmaceutical compositions containing combinations of metformin with a fibrate, especially fenofibrate or bezafibrate are known from WO 99/40904. Due to the combination of the active ingredients the cholesterol level and the trigliceride level can also be reduced by the treatment besides the reduction of blood glucose, the reduction of the blood glucose, however, does not attain the desired extent.

A further disadvantage of the metformin therapy is that metformin should be administered in controlled quantities due to risk factors (lactic acidosis) and unfavorable side effects, mainly certain gastrointestinal problems. Thus, decreasing the relative amount of metformin is desirable in pharmaceutical compositions containing metformin in combinations. Such an endavour appears from WO 97/17975 mentioned above.

In the therapy of type II diabetes mellitus based on the simultaneous application of metformin and an other antihyperglycemic agent there is a need of a combination of active agents which provides a stronger reduction of blood glucose level, makes possible the decrease of the amount of metformin administered and has the slightest possible side effect.

Disclosure of the invention

The invention provides a new pharmaceutical composition which is orally applicable in the treatment of diabetes mellitus which comprises a combination of metformin (N,N-dimethylimido-dicarbonimidic diamide) or an acid addition salt thereof and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or an acid addition salt of the racemic or the optically active form thereof as active ingredient, if necessary, together with pharmaceutically acceptable carriers and optionally auxiliary materials.

It has been found that by combining metformin and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride, in certain models the combination of the said two active agents exerts a very strong blood glucose lowering effect. This effect makes the combination of the two active agents capable of normalizing the fasting blood glucose and radically reducing or even normalizing the postprandial blood glucose level.

Moreover, the combination of metformin and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride proved to be effective in the curative treatment of peripheral diabetic neuropathy. Unexpectedly, we have found that the antineuropathic efficacy of N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride is synergistically enhanced when this compound is applied in combination with metformin.

Based on this recognition the invention provides an orally applicable pharmaceutical composition for the treatment of diabetic neuropathy which comprises as active principle a combination of metformin (N,N-dimethylimido-dicarbonimidic diamide) or an acid addition salt thereof and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or an acid addition salt of the racemic or the optically active form thereof.

The N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride and the preparation of this compound and its optically active enantiomers are described in WO 00/50403. As it appears therefrom, this compound is effective against insulin resistance and useful mainly in the treatment of chronic complications of diabetes mellitus (e.g. neuropathy) with simultaneous lowering of insulin resistance.

According to the present invention metformin is preferably present in the composition as an acid addition salt formed with a mineral or organic acid such as hydrochloric, hydrobromic, acetic, lactic, oxalic, maleic, malonic, succinic, fumaric, citric, methanesulfonic and p-toluenesulfonic acid, where the hydrochloride and the fumarate are preferred. Similarly, the N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride is preferably present in the composition of the invention in the form of an acid addition salt formed with a mineral or organic acid, such as hydrochloric, hydrobromic, maleic, fumaric, p-toluenesulfonic, methanesulfonic, citric and tartaric acid, preferably in the form of hydrochloride, citrate or maleate.

Preferably an optically active enantiomer of the N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride is present in the composition of the invention. According to the invention the most preferred composition contains an acid addition salt of metformin and (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate as active ingredients.

The weight ratio of metformin to the N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride varies preferably between 5:1 and 100:1. In compositions for use in the therapy of diabetes mellitus, the preferable weight ratio of metformin to N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride ranges from 10:1 to 50:1. In compositions for use in the treatment of diabetic neuropathy a weight ratio of metformin

to N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride ranging from 25:1 to 75:1 is preferable.

The pharmaceutical composition of the invention is prepared by mixing the two active principles and vehicles and optionally auxiliary materials usually applied in the pharmaceutical industry in a conventional way. The compositions of the invention are formulated for oral application into tablets, coated tablets, dragées, granulates, capsules, solutions or syrups. The solid forms of the composition can contain fillers, such as microcrystalline cellulose, starch and lactose, lubricants, such as stearic acid and magnesium stearate, coating materials, such as sugar, film forming materials, such as hydroxymethyl cellulose or hydroxypropyl methyl cellulose as well as conventional flavours and colors. The capsule formulations can be prepared with use of hard or soft gelatin capsules.

Preferably, the pharmaceutical compositions of the invention are prepared in unit dosage forms for administering two or three times per day. The daily dose of metformin is preferably 1000-2000 mg, that of N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride is preferably 2-100 mg, the exact dose depending on the weight and age and the condition of the patient. These amounts are calculated for the base form of the active principles. One unit dosage form contains the corresponding amounts of active agents, the metformin preferably as an acid addition salt thereof and the N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride preferably in the form of an acid addition salt of an optically active enantiomer thereof.

The invention also relates to a method of treatment of diabetes mellitus comprising the administration of a combination of metformin (N,N-dimethylimido-dicarbonimidic diamide) or an acid addition salt thereof and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or an acid addition salt of the racemic or the optically active form thereof to the patient.

Further, the invention provides a method of treatment of diabetic neuropathy comprising the administration of a combination of metformin (N,N-dimethylimido-dicarbonimidic diamide) or an acid addition salt thereof and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or an acid addition salt of the racemic or the optically active form thereof to the patient.

The N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride alone in lower doses does not possess a considerable antihyperglycemic effect. In the tests reported in the above cited WO 00/50403 a moderate antihyperglycemic effect was observed only on genetically leptin-deficient ZDF rats. However, when applied in combination with metformin, a very strong blood glucose lowering effect can be observed, which is manifested in a radical reducing both of fasting and postprandial blood glucose level. As it appears clearly from the data of our experiments described below, the combination of the two said active agents results in a synergistic increase of biological activity. The experimental study of peripheral neuropathies has also revealed that the curative effect of N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride is synergistically enhanced when applying a combination of metformin and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride in the treatment of diabetic neuropathy.

The experiments for studying the biological acitivity of the active agents are reported in the following.

Study of blood glucose level on STZ diabetic rats

Groups of male Wistar rats of 300-350 g body weight, at least 6 animals in each group were used in the experiments. The animals fasting at least 14 hours were treated intravenously with 40 mg/kg streptozotocin (STZ) freshly dissolved in physiological saline in order to induce diabetes. The concentration of the stock solution was 40 mg/ml and the applied amount was 0,1 ml/100g.

For checking whether diabetes had developed the animals were placed in rat stocks after a period of 24 hours following the STZ treatment. 1-1,5 mm of tips of tails were cut by scissors and at least 200 µl blood samples were taken into Eppendorf tubes. The blood samples were centrifuged at 2500 rpm while cooling (4 °C). In the obtained sera the blood glucose levels were measured by Vitros 250 automatic analyzer. Animals having a nonfasted serum glucose level over 15 mmol/liter were considered diabetic.

N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride (referred to as compound A in the followings) was applied orally in 12 mg/kg doses (calculated for the base). Metformin was applied in 250 mg/kg p. o. doses. One group of animals was treated with compound A alone, other groups were treated with metformin and a combination of metformin and compound A, respectively, for 1 month after the time of demonstrating that diabetes had been developed.

At the end of period of treatment 0,5 ml blood was taken gently from the conscious animals fasting at least 14 hours, sera were obtained in the way described above and blood glucose levels were measured with automatic analyzer. The results of the determination are shown in Table 1. The obtained data are expressed in mean ± SE form. The table contains the values of Student's impaired „t" test obtained when comparing the individual groups.

Table 1

Group of animals (n = 7)		Serum glucose (mmol/l)	
		Test compound	Test compound + metformin
Wistar control			
	mean ± SE	**6.61 ± 0.23**	
STZ control			
	mean ± SE	**25.11 ± 2.49**	

	p *vs.* Wistar	0.00001	
STZ + Metformin 250 mg/kg	mean ± SE	**17.74 ± 1.65**	
	p *vs.* STZ	0.09	
	p *vs.* Wistar	2.9×10^{-5}	
STZ + compound A 12 mg/kg	mean ± SE	**22.62 ± 2.28**	**5.3 ± 0.57**
	p *vs.* STZ	0.58	6.8×10^{-5}
	p *vs.* metformin		1.1×10^{-4}

Study of glucose tolerance on GK rats

Goto Kakizaki (GK) inbred rat strain is selectively bred from normal outbred Wistar rats for high glucose levels. It is a widely accepted animal model for research in type II diabetes mellitus. (Motoy Koyama et al: American Journal of Pathology 153 (2) 537-545, 1988; Metabolism 49 (3) 347-352, 2000).

Twelve weeks old GK rats were treated orally with 5 mg/kg compound A, oral doses of 150 mg/kg, 200 mg/kg and 250 mg/kg of metformin, and combinations of compound A and metformin in the enumerated doses. The oral glucose tolerance test has been made after a 1 month treatment period.

Overnight (min 14 hours) fasted rats were treated with 1 g/kg glucose orally. Blood samples were taken from the animals before and after 5, 10, 30, 60 and 120 minutes of oral glucose load. Blood samples were held in ice cold bath while centrifugation (2000 rpm; 4 °C; 20 min). Serum glucose levels were measured by Vitros 250 automatic analyzer. Area under curves (AUC) were determined individually on the basis of glucose curves. The results are summarized in Table 2.

Table 2

Group of animals (n = 6)		**AUC glucose (120 min)**
Wistar control		
	mean ± SE	**1304.34 ± 105.2**

GK control		
	mean ± SE	**2886.32 ± 103.74**
	p *vs.* Wistar	0.036
Compound A	mean ± SE	**3041.97 ± 202.86**
	p *vs.* GK	0.51
5 mg/kg	p *vs.* metformin	0.00096
Metformin 250 mg/kg	mean ± SE	**2115.76 ± 0:51**
	p *vs.* GK	4.16×10^{-5}
Metformin 250 mg/kg	mean ± SE	**1620.75 ± 155.37**
+ Compound A	p *vs.* GK	1.97×10^{-5}
	p *vs.* metformin	0.013
5 mg/kg	p *vs.* Wistar	0.12
Metformin 200 mg/kg	mean ± SE	**2334.59 ± 297.64**
	p *vs.* GK	0.11
Metformin 200 mg/kg	mean ± SE	**2247.72 ± 128.96**
+ Compound A	p *vs.* GK	0.0032
	p *vs.* metformin	0.81
5 mg/kg		
Metformin 150 mg/kg	mean ± SE	**2506.07 ± 135.28**
	p *vs.* GK	0.04
Metformin 150 mg/kg	mean ± SE	**1990.74 ± 144**
+ Compound A	p *vs.* GK	0.0003
	p *vs.* metformin	0.024
5 mg/kg		

As it appears from the above experiments the fasting glucose level is not only reduced significantly, but is normalized by N-[2-hydroxy-3-(1-piperidinyl)-

propoxy]-pyridine-1-oxide-3-carboximidoyl chloride when it is added together with metformin. It is demonstrated in a further experiment that N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride reduces not only the fasting glucose but the postprandial glucose as well when administered together with metformin in a type II diabetes model (GK rats) while in itself it does not lower the blood glucose levels. The interaction comes into existence even when the dosis of metformin is reduced around to the half of the original (150 mg/kg) which is no more capable of lowering the blood glucose level significantly so that metformin is applicable in the therapy without the risks and unfavorable side effects accompanying the application of metformin.

Electrophysiological examination of peripheral neuropathy

To check the presence and the measure (degree) of peripheral neuropathies in normal and diabetic rats (Goto Kakizaki (GK) rats), spinal reflexes of hind limbs are studied by using a combined noninvasive electrophysiological method. Under i.p. anesthesia (400-340 mg/kg urethane and 80-70 mg/kg α-chloralose mixture) nerve conduction velocities in large myelinated fibres of the mixed-type sciatic nerve are measured simultaneously with the skin sensory function of the small fibres before and at the end of the treatment period. Monosynaptic extensor reflexes (ER) recorded to sciatic and tibial nerve stimulation serve for determination of muscle motor (MNCV) and sensory (SNCV) nerve conduction velocities (NCVs). The polysynaptic nociceptive flexor reflex (FR) to electric stimulation of the plantar surface is used to measure skin sensory function of small fibres.

Supramaximal stimuli are delivered through needle electrodes by a Nihon-Kohden (model SEN-3201, Japan) stimulator. Evoked electromyograms (EMGs) are amplified (Iso-Dam Isolated Biological Amplifier, WPI, World Precision Instruments, Inc. U.S.A.), averaged and stored (IBM compatible PC) to analyse the curves by experimentor blind to the treatment identity.

For recording of extensor reflex (ER), the two point stimulation method of Stanley (*1981 Exp Neurol 71: 497-506*) modified by De Koning and Gispen (*1987*

Peptides 8: 415-422) is used to record electromyographic signs of ER (ER-EMG) which are necessary for NCV determination. The sciatic and tibial nerves of the left hind limb are electrically stimulated (square wave impulses of supramaximal intensity and 0.03 ms width) at sciatic notch or ankle, respectively (SOP No: PRE NP 022, 2002). After recording of responses the distance between the two stimulation points are measured.

Each EMG consists of two components: 1/ the short-latency direct motor response (M) evoked by stimulation of A-α motor fibres and 2/ the monosynaptically elicited Hoffmann reflex response (H) due to activation of proprioceptive afferents. Latency of both the M- and H- components of EMG, taken from plantar muscles, are measured for calculation of MNCV and SNCV.

For recording of flexor reflex (FR), the method of *Turski et al. (1990 Neurosci Lett 113: 66-71*) is applied to monitor changes in sensory function of the footsole (SN) in rats. Electrical stimuli strong enough to recruit thinly myelinated and unmyelinated nerves, originating in skin, evoke FR. Subcutaneous stimulating electrodes are used for stimulation of sural and tibial nerve terminals of the paw (*De Koning P et al. 1986 J Neurological Sci 74: 237-246*). Short trains of five impulses of 0.3 ms duration are delivered at 500 Hz frequency and repeated 7 times. Bipolar needle electrodes serve to record EMG activity from the tibial anterior muscles of hind limb.

EMG responses are analysed by means of Matlab software (The MathWorks, Inc., Natick, Mass., USA).

For calculation of NCVs 5-5 stored ER-EMG curves, recorded from plantar muscles, are averaged. Latencies of M- and H-components are established. NCVs are calculated by using the following formulas: MNCV = distance between the sciatic and tibial stimulation points divided by differences of latencies for $M_{sciatic}$ and M_{tibial}; SNCV = distance between the sciatic and tibial stimulation points divided by differences of latencies for H_{tibial} and $H_{sciatic}$.

After rectification, 7-7 FR-EMG curves are averaged for determination of SN. The subcurve areas bounded by rectified and averaged EMGs and the baselin e are established before and after treatments. Depression in integrated subcurve areas (the magnitude of FR-EMG response), due to SN (diabetic deficit), as well as the improvements caused by treatments are calculated.

Statistical analyses were carried out by Graphpad Instat (San Diego, U.S.A.) statistical program package. NCVs and FR-EMG areas are expressed as means ±SE, with significance set at $p<0.05$. One way ANOVA (with Tukey-Kramer multiple comparisons test) is used for parametric values, and Kruskal-Wallis nonparametric ANOVA test (with Dunn's multiple comparisons test) is carried out for comparison of nonparametric values. Reduction (deficit) in NCVs, due to neuropathy, and their recovery (improvement) caused by treatments, are presented in percentage. At least 7 animals were in each group.

Table 3

Effects of curative treatments on peripheral neuropathies of sciatic nerve in GK rats

GROUPS	NERVE CONDUCTION VELOCITIES							
	M N C V				S N C V			
	W0 m/s	*Deficit %*	W6 m/s	Impr. %	W0 m/s	*Deficit %*	W6 m/s	*Impr. %*
Healthy control (C)	61.0 ± 0.3		61.3 ± 0.2		63.1 ± 0.3		63.7 ± 0.3	
GK-diabetic (GK)	49.2 ± 0.3^{+++}	***19.3***	48.3 ± 0.3^{+++}	***•21.2***	50.4 ± 0.4^{+++}	***20.1***	49.7 ± 0.3^{+++}	***•22.0***
GK+Nateglinide 50 mg/kg (GKT1)			54.4 ± 0.4***	**46.9**			56.3 ± 0.4***	**47.1**

GK+Metformin 250 mg/kg (GKT2)			51.1 ± 0.4***	**21.5**			53.1 ± 0.4***	**24.3**
GK+ Compound A (base) 4 mg/kg (GKT3)			56.6 ± 0.2***	**63.8**			58.9 ± 0.1***	**65.7**
GK+Metf. 250 mg/kg + Comp. A (base) 4mg/kg (GKT4)			59.5 ± 0.3***	**86.2**			62.0 ± 0.3***	**87.9**

+++ $p < 0.001$ v.s. Healthy control at W0 and W6
*** $p < 0.001$ **v.s. GK-diabetic at W6**

- diabetic deficits at W6 in saline-treated GK controls

$p < 0.001$ GKT2 v.s. GKT3
$p < 0.001$ GKT2 v.s. GKT4
$p < 0.001$ GKT3 v.s. GKT4

Table 4

Effects of 6-week treatments on small fibre sensory neuropathy of GK rats

Measurement	No	*MEAN*	±SE	*Deficit%*	Improv.%
HEALTHY CONTROL (C)					
W0	6	985249.5	5695.5		
W6	8	1013820.4	9040.6		
GK DIABETIC CONTROL (GK)					
W0	7	803166.1	8686.7	*18.5*+++	
W6	8	713374.6	10395.0	*29.6*+++	
GK treated with Nateglinide (GKT1)					
W6	7	872728.3	7174.3		53.0***
GK treated with Metformin (GKT2)					
W6	7	848123.8	7988.5		44.9***

GK treated with Compound A (GKT3)					
W6	7	933321.1	6461.4		73.2***
GK treated with Metformin + Compound A (GKT4)					
W6	6	988161.6	10197.0		91.5***

Using parametric One-way ANOVA with Tukey-Kramer Multiple Comp. Test

+++ $p < 0.001$ v.s. Healthy control at W0 and W6

*** $p < 0.001$ **v.s. GK diabetic at W6**

$p < 0.001$ GK at W0 v.s. at W6

$p < 0.001$ GKT2 v.s. GKT4

$p < 0.01$ GKT3 v.s. GKT4

Using Kruskal-Wallis Nonparametric ANOVA Test with Dunn's Multiple Comp. Test

*** $p < 0.001$ **v.s. GK diabetic at W6** only for GKT3 and GKT4;

$p < 0.01$ GKT2 v.s GKT4

The invention is illustrated by the following examples.

Example 1

Tablet

Tablets are prepared with the following composition:

metformin hydrochloride	500 mg
(+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate	10 mg
polyvinyl pyrrolidone	20 mg
croscarmellose sodium	55 mg
magnesium stearate	9 mg
micorcrystalline cellulose	75 mg

Metformin hydrochloride, (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate, around a half of microcrystalline cellulose and croscarmellose sodium are blended in a planetary mixer. An aqueous solution of polyvinyl pyrrolidone is added and the mixture is wet granulated. The granules are dried at 60 °C, sieved and introduceed into a cone

blender. Magnesium stearate and the remaining portion of microcrystalline cellulose are added and the mixture is homogenized. The mix is filled in a tablet press and formed into tablets.

Example 2

Capsule

Capsulated medicine is prepared with the following composition:

metformin hydrochloride	250 mg
N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate	50 mg
polyvinyl pyrrolidone	20 mg
starch	25 mg
talc	3 mg
lactose	80 mg

The active principles, the fillers and the auxiliaries are blended in a planetary mixer and the mixture is wet granulated with water. The granules are dried at 60 °C and sieved. The granules are filled into hard gelatine capsules.

Example 3

Coated tablet

Coated tablets are prepared with the following composition:

metformin hydrochloride	800 mg
(+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride hydrochloride	10 mg
polyvinyl pyrrolidone	20 mg
croscarmellose sodium	15 mg
microcrystalline cellulose	55 mg
magnesium stearate	10 mg
hydroxypropyl methylcellulose (film coating)	12 mg

The tablets are prepared as described in Example 1. Granules are prepared by wet granulating from the active principles and the required auxiliary

materials. The granules are mixed with the tabletting materials and pressed into tablets. The tablets are coated with hydroxypropyl methylcellulose film.

Claims

1. An orally applicable pharmaceutical composition for the treatment of diabetes mellitus comprising as active principle a combination of metformin (N,N-dimethylimido-dicarbonimidic diamide) or an acid addition salt thereof and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or an acid addition salt of the racemic or the optically active form thereof.

2. Pharmaceutical composition according to claim 1 wherein the weight ratio of metformin or the acid addition salt thereof to the N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or the acid addition salt of the racemic or the optically active form thereof is between 5:1 and 100:1.

3. Pharmaceutical composition according to claim 2 wherein the weight ratio is between 10:1 and 50:1.

4. Pharmaceutical composition according to any one of claims 1 to 3 containing as active principle an optically active enantiomer of N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride combined with metformin.

5. Pharmaceutical composition according to claim 4 containing as active principle (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate combined with a metformin salt.

6. Method of treatment of diabetes mellitus comprising the administration of a combination of metformin (N,N-dimethylimido-dicarbonimidic diamide) or an acid addition salt thereof and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or an acid addition salt of the racemic or the optically active form thereof to the patient.

7. An orally applicable pharmaceutical composition for the treatment of diabetic neuropathy comprising as active principle a combination of metformin

(N,N-dimethylimido-dicarbonimidic diamide) or an acid addition salt thereof and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or an acid addition salt of the racemic or the optically active form thereof.

8. Pharmaceutical composition according to claim 7 wherein the weight ratio of metformin or the acid addition salt thereof to the N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or the acid addition salt of the racemic or the optically active form thereof is between 5:1 and 100:1.

9. Pharmaceutical composition according to claim 8 wherein the weight ratio is between 25:1 and 75:1.

10. A pharmaceutical composition according to any one of claims 7 to 9 containing as active principle an optically active enantiomer of N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride combined with metformin.

11. A pharmaceutical composition according to claim 10 containing as active principle (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximid-oyl chloride citrate combined with a metformin salt.

12. Method of treatment of diabetic neuropathy comprising the administration of a combination of metformin (N,N-dimethylimido-dicarbonimidic diamide) or an acid addition salt thereof and N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride or a stereoisomer thereof or an acid addition salt of the racemic or the optically active form thereof to the patient.

INTERNATIONAL SEARCH REPORT

al Application No
PCT/HU 02/00098

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4545 A61K31/155 A61P3/10 //(A61K31/4545,31:155)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 50403 A (SZILBEREKY JEN & ODBLAC ;CSAKAI ZITA (HU); KUERTHY MARIA (HU); MAR) 31 August 2000 (2000-08-31) cited in the application claims 1-7 ---	1-12
P,Y	WO 01 79174 A (JEGESNE CSAKAI ZITA ;SZAKACSNE SCHMIDT ANIKO (HU); TOEMOESKOEZI IS) 25 October 2001 (2001-10-25) claims 1-9 --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 December 2002	19/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herrera, S

INTERNATIONAL SEARCH REPORT

ıal Application No
PCT/HU 02/00098

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	ZIMMET P ET AL: "CLINICAL EFFICACY OF METFORMIN AGAINST INSULIN RESISTANCE PARAMETERS SINKING THE ICEBERG" DRUGS, ADIS INTERNATIONAL LTD, AT, vol. 58, no. SUPPL 1, 1999, pages 21-28, XP000913604 ISSN: 0012-6667 abstract	1-12

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/HU 02/00098

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 6 and 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

ial Application No
PCT/HU 02/00098

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0050403 A	31-08-2000	AU	3182400 A	14-09-2000
		BG	105837 A	29-03-2002
		BR	0008969 A	27-11-2001
		CZ	20013053 A3	16-01-2002
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WO 0179174 A	25-10-2001	HU	0001583 A2	28-11-2002
		AU	5499701 A	30-10-2001
		WO	0179174 A1	25-10-2001